REMARKS

A. Status of the Claims

Claims 24-34 are pending in the application. The present Action withdrew claims 24-32 from consideration and examined claims 33 and 34. Claims 33 and 34 were rejected. Claims 33 and 34 have been amended to specify that the transgenic animal is a "non-human" animal. Support for this amendment may be found in, for example, paragraph [0225] (as numbered in U.S. Publication 2006/0167227).

B. Restriction Requirement

The Action maintains the restriction requirement between the Group I and Group II inventions on grounds that the doubly truncated tau protein does not define a contribution over the art of Ghetti *et al.* or WO 96/30766. The Action's position in this regard is incorrect.

Ghetti discloses a full-length tau sequence; it does not disclose N- and C-terminally double truncated type IA, IB, IIA, or IIB tau molecules as recited in the claims. The double truncations are defined in the specification for each of the type IA, IB, IIA, and IIB tau molecules (*see*, p. 6, 7, 8, and 8-9, respectively). By way of illustration, the specification discloses that type IIA tau molecules have at least the first 68 N-terminal amino acids and at least the last 40 C-terminal amino acids of 4 repeat containing tau43 or the first 68 N-terminal amino acids and at least the last 20 C-terminal amino acids of the 3 repeat containing tau44 truncated (Specification, p. 8).

The claims should be read in light of the specification, but it appears that the Examiner has failed to do so here. The type IA, IB, IIA, and IIB tau molecules described in the present specification are not disclosed by Ghetti. Furthermore, it is clear from the specification that a three-repeat tau protein is not a C-terminal truncation of a four-repeat tau protein as alleged in the Action.

The sequence identified by the Examiner in WO 96/30766 appears to correspond to the tau core fragment disclosed by Novak *et al.* (1993) (IDS ref. C8), which is discussed on page 4 of the present specification. Further studies of this tau core fragment were described by Fasulo et al. (1996), which is also discussed on page 4 of the present specification. This tau core fragment, which is also referred to as dGAE, can be distinguished structurally and functionally from the type IA, IB, IIA, and IIB tau molecules described in the present specification.

The dGAE sequence of WO 96/30766 was only produced *in vitro* and thus has no direct connection to Alzheimer's disease. WO 96/30766 is focused on tau-tau-interaction – in particular the interaction of dGAE with full length tau and using it as a drug screening tool for compounds able to disassemble tau–tau associations. The tau molecule according to SEQ ID NO: 1 of the present application, however, does not interact with normal healthy tau, nor does it bind to microtubuli in vitro or in vivo.

In addition, the enclosed declaration of Dr. Novák shows that type IA tau molecules are conformationally different from the fragment mentioned in WO 96/30766. The Novák Declaration describes the results of studies comparing the ability of monoclonal antibodies DC-11, DC-25, and DC-44, to bind to normal tau and truncated tau. The DC-11 and DC-44 monoclonal antibodies specifically bind to a truncated tau molecule, but do not bind to normal human tau protein (Novák Declaration, para. 4). DC-25 is a pan-tau antibody that binds to both normal and truncated tau molecules (Novák Declaration, para. 4). Monoclonal antibodies DC-44 and DC-11 discriminated between recombinant dGAE as disclosed in WO 96/30766 and tau type IA fragments derived from brain tissue (Novák Declaration, para. 5 and 6). Pan-tau monoclonal antibody DC-25 recognized both forms of the tau protein (Novák Declaration, para. 5 and 6).

Moreover, functional distinction between SEQ ID NO: 1 and dGAE in WO 96/30766 can be made at the level of microtubuli binding activity as described by Fasulo et al. Fasulo discloses

that dGAE cannot bind microtubuli either in vitro or in vivo (*see e.g.,* Abstract; p. 197, last sentence). Fasulo and colleagues furthermore mention that the particular form of tau truncation (referred to as core fragment dGAE), per se is not sufficient to induce tau aggregation and its assembly into PHFs (*see e.g.,* Abstract). In contrast, the present application shows that pathological tau type IA is able to interfere in vivo and in vitro with microtubuli (Example 2).

Thus, the doubly truncated tau protein of the Group I and Group II inventions does define a contribution over the art of Ghetti *et al.* or WO 96/30766. Applicant, therefore, requests the withdrawal of the restriction requirement.

C. Claim Rejections Under 35 U.S.C. § 112

The Action rejects claims 33-34 under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Action acknowledges that the specification is enabling for making a transgenic mouse comprising a genome having a double truncated tau sequence integrated therein, but argues that the specification does not reasonably enable making a transgenic animal of any species, wherein the genome of the animal comprises a double truncated tau sequence integrated therein and further wherein the animal exhibits Alzheimer's disease associated risk factors. Applicant traverses this rejection.

The current claims are directed to a non-human transgenic animal expressing an N- and C-terminally double truncated tau molecule further defined as a type IA tau molecule, type IB tau molecule, type IIA tau molecule, or type IIB tau molecule; and a method of screening or testing a candidate compound for utility in the treatment of Alzheimer's disease comprising obtaining the non-human transgenic animal and using the animal to screen or test the candidate compound. The structure and function of the type IA, IB, IIA, and IIB tau molecules are described in the specification (see e.g., p. 6, 7, 8, and 8-9, respectively). Example 14 discloses a method for generating transgenic animals by pronuclear injection. In addition, Example 14 discloses

genotyping by specific amplification of transgenes encoding double truncated tau to identify transgenic animals.

Applicant provides the declaration of Dr. Filipcik ("Filipcik Declaration") as further evidence that a person skilled in the art is able to produce transgenic animals with predictable phenotype using gene constructs described in the present application. The Filipcik Declaration describes studies in which it is clearly shown that the phenotype induced by the transgenes, which are truncated tau, is robust, highly reproducible and predictable. Several independent transgenic lines (Tg line #318, Tg line #72 and Tg line #24) were generated using DNA gene constructs encoding proteins, which have shown neurofibrillary (NF) pathology producing activity when expressed in brain cells (Filipcik Declaration, para. 4). In addition, transgenic line SHR24/72 was created by crossing Tg line #72 and Tg line #24 (Filipcik Declaration, para. 13). The transgene construct used in the generation of transgenic rat lines #318 and #72 encodes a truncated tau protein of amino acids 93-333, which correspond to nucleotides 279-999, based on the numbering for the four-repeat containing tau 43 isoform (Filipcik Declaration, para. 4). The normal tau 43 protein is 383 amino acids (Filipcik Declaration, para. 4). Thus, as described in the present patent application for the type IIA and IIB tau molecules, the truncated tau protein expressed in rat lines #318 and #72 has at least the first 68 N-terminal amino acids and at least the last 40 C-terminal amino acids of the four-repeat tau 43 truncated (Filipcik Declaration, para. 4).

The transgene construct used in the generation of transgenic rat line #24 encodes amino acids 93-302, which correspond to nucleotides 277-906, based on the numbering used for isoform 44 (3-repeat tau) (Filipcik Declaration, para. 5). The normal tau 44 protein is 352 amino acids (Filipcik Declaration, para. 5). Thus, as described in the present patent application for the type IIA and IIB tau molecules, the truncated tau protein expressed in rat line #24 has at least the

first 68 N-terminal amino acids and at least the last 20 C-terminal amino acids of the three-repeat tau 44 truncated (Filipcik Declaration, para. 5).

The progress of sensory-motor impairment of animals from transgenic line #318 and transgenic line #24 is almost identical, and the onset and progression of neurodegeneration is the same in all three transgenic rat lines (Filipcik Declaration, para. 6). The only observed difference being the strength of the resulting phenotype when comparing Tg line #72 and Tg line #24 (Filipcik Declaration, para. 6). While behavioral features are almost the same, the life span of those animals containing 4 repeat tau (e.g. Tg line #72) is much shorter when compared to those animals containing 3 repeat tau region (e.g. Tg line #24) of human tau protein (Filipcik Declaration, para. 6).

Transgenic rat lines #318 and #24 exhibit neurofibrillary (NF) pathology. Transgenic rat line #24 developed neurofibrillary lesions in the brain stem, spinal cord, primary motor cortex, and hippocampus (Filipcik Declaration, para. 7). Neurological examinations showed that the progress of sensory-motor impairment of animals from transgenic line #318 and transgenic line #24 was almost identical (Filipcik Declaration, para. 8). Moreover, the transgene was transmitted to subsequent offspring generations and the phenotype remained unchanged even in the 4th generation of offspring (Filipcik Declaration, para. 8). In addition, transgenic rats from line #24 suffer from early cognitive impairment as demonstrated in the object recognition test (Filipcik Declaration, para. 9).

It was also determined that the final neurofibrillary tangle (NFT) load in the terminal stage of life of the transgenic animal lines was independent of expression level (Filipcik Declaration, para. 10). Moreover, the observed phenotype of the transgenic rats was not dependent on genetic background. After the transfer of the transgene from the genetic background of the hypertensive SHR strain into the normotensive Wistar strain (WKY), an

almost the identical phenotype was observed at the level of biochemical examination as well as in behavioral measurements (Filipcik Declaration, para. 12). Furthermore, by crossing transgenic lines 24 and 72 transgenic line expressing both 3R and 4R human truncated tau proteins was created (Filipcik Declaration, para. 13). The resulting phenotype was synergistic in the rats expressing human truncated tau with 4 and 3 repeats (Filipcik Declaration, para. 13).

Neurofibrillary pathology is the most important and earliest immunohistochemical finding in Alzheimer's disease; and, therefore, an animal model that exhibits neurofibrillary pathology is a useful model of Alzheimer's disease (Filipcik Declaration, para. 14). The three transgenic rat lines described in the Filipcik Declaration exhibit an aggressive neurodegenerative phenotype resembling fundamental neuropathological features of brain typical for Alzheimer's disease sufferers (Filipcik Declaration, para. 14). Furthermore, these phenotypes were independent of transgene expression level and genetic background (Filipcik Declaration, para. 14). In addition, the phenotypes were stable even after several years of continual breeding (Filipcik Declaration, para. 14).

In addition to rats, a variety of animal models would be suitable Alzheimer's disease (AD) models since AD associated neurofibrillary (NF) pathology, based on paired helical filaments (PHF), occurs in a number of animals. For example, Hartig et al. (European Journal of Neuroscience, Vol. 25, pp. 69–80, 2007) shows that PHF-like tau occurs in hamsters, which parallels the situation in AD (abstract). Hartig also notes that PHF-like tau was observed in ground squirrels (p. 69, right col., para. 2).

Huang et al., (Brain Research 771, 1997, 213 –220) describes neurofibrillary tangles based on abnormal tau in rabbits. The proteins have a molecular structure that closely resembles that of primates, thus making such an animal system of relevance for human neurodegenerative disease like AD (abstract, p. 214, left col., para. 2, p. 219, left col., para. 2).

Gotz (Brain Research Reviews 35 (2001) 266–286) describes the use of murine models expressing tau as system for the dysfunction of tau and neurodegeneration and dementia based on neurofibrillary lesions (abstract, p. 275, right col., item 4.3). In addition, Lewis et al., (Nat Genet. 2000 Aug; 25(4):402-5)) describes the formation of AD related NF tangles through expression of mutant human tau in mice (abstract). These references demonstrate that a variety of animals are capable of exhibiting NF pathology and, therefore, are suitable for the study of NF pathology and Alzheimer's disease.

In view of the above, the claims are enabled for non-human transgenic animals and the evidence demonstrates that such animals exhibit characteristics that make them suitable models for Alzheimer's disease.

D. Double Patenting

Claims 33-34 are provisionally rejected for nonstatutory obviousness-type double patenting over claims 17-21 of copending Application No. 10/521,049. A provisional double-patenting rejection, however, is not a final rejection that blocks the prosecution of all of the conflicting applications. If a provisional double-patenting rejection is the only rejection remaining in an application, the Examiner should withdraw the rejection and permit the application to issue as a patent. MPEP § 804(I)(B). After one application issues as a patent, the provisional double-patenting rejection in the remaining application is converted to an actual double patenting rejection. Id. Thus, either the present application or the '049 application must issue as a patent before an actual double patenting rejection may be raised against the remaining application. Applicant will file a terminal disclaimer, if appropriate, at that time.

E. Conclusion

Applicant believes that these remarks fully respond to all outstanding matters for this application. Applicant respectfully requests that the rejections of all claims be withdrawn.

Respectfully submitted,

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